IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF OKLAHOMA

ANNABEL DOBBS, Individually and as Personal Representative of the Estate of TERRY DOBBS, Deceased,	)	
Plaintiff,	)	
vs.	)	Case No. CIV-04-1762-F
WYETH PHARMACEUTICALS,	)	
Defendant.	)	

ORDER

Before the Court is the renewed motion for partial summary judgment (doc. no. 266) of Defendant Wyeth Pharmaceuticals ("Wyeth"). The renewed motion was filed following the Tenth Circuit's decision vacating the court's January 17, 2008 Order[1] granting Wyeth's motion for partial summary judgment based on the conclusion that plaintiff's common law failure-to-warn claims are preempted by the United States Food and Drug Administration ("FDA") regulations governing the content of labels accompanying FDA-approved prescription drugs.

While plaintiff's interlocutory appeal of the summary judgment order was pending, the United States Supreme Court issued its decision in *Wyeth v. Levine*, 555 U. S. 555, 129 S.Ct. 1187 (2009). Because *Levine* announced a "clear evidence" standard of proof required to support a claim of conflict preemption based on FDA labeling regulations, the Tenth Circuit vacated the summary judgment ruling and remanded the case for the purpose of determining whether Wyeth can present clear

[1]*Dobbs v. Wyeth Pharmaceuticals*, 530 F. Supp. 2d 1275 (W. D. Okla. 2008).

evidence to support its preemption claim. *Dobbs v. Wyeth Pharmaceuticals*, 606 F. 3d 1269, 1270 (10th Cir. 2010). The Court of Appeals instructed this court to permit the parties to submit additional evidence and to then reconsider the preemption issue "in light of *Levine's* new 'clear evidence' standard." *Id.* The parties have now filed supplemental briefs and submitted evidence in support of their respective positions.

Background:

Plaintiff brought this action to recover damages resulting from the 2002 suicide of her 53-year-old husband, Terry Dobbs. Plaintiff alleges that Mr. Dobbs, who had been diagnosed with depression, committed suicide as a result of taking Effexor, an antidepressant drug prescribed by his treating physician. Effexor is manufactured by Wyeth and was approved by the FDA in 1993. In 2002, Effexor's labeling and package insert included an FDA-approved statement regarding suicidality in patients diagnosed with depression. However, plaintiff contends the information was inadequate to warn Mr. Dobbs of the risk of suicide associated with Effexor, and alleges Wyeth breached its common law duty to fully warn of that risk. She asserts Oklahoma tort claims based on strict liability for failure to warn, negligent failure to warn, and misrepresentation.

Wyeth sought judgment on the failure-to-warn claims, arguing that the claims are preempted by regulations requiring FDA approval of the content of warnings contained in prescription drug labels. Wyeth argued that, in 2002, the FDA had concluded that a more extensive suicidality warning for Effexor and other antidepressants was not supported by scientific evidence, and it would not have approved the warning which plaintiff contends is required by Oklahoma law. Thus, Wyeth argued it could not comply with the common law duty urged by plaintiff and the FDA regulations without risking potential adverse action by the FDA.

In granting the motion and concluding that the failure-to-warn claims are preempted by the FDA regulations, the court limited its ruling to the specific facts of this case. It concluded that the undisputed evidence showed "the express type of warning which plaintiff claims Defendant should have included in its Effexor label had been considered and rejected by the FDA as not supported by credible evidence at the time Mr. Dobbs used Effexor." *Dobbs*, 530 F. Supp. 2d at 1289. The issue now before the court is that conclusion is supported by clear evidence.

Summary judgment standard:

Summary judgment may be granted where the undisputed material facts establish that one party is entitled to judgment as a matter of law. Fed.R.Civ.P. 56; *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). A material fact is one which may affect the outcome of the suit under the governing law. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48 (1986). To avoid summary judgment, a plaintiff must present more than a "mere scintilla" of evidence; the evidence must be such that "a reasonable jury could return a verdict for the non-moving party." *Id.* The facts in the record and reasonable inferences therefrom must be viewed in the light most favorable to the nonmoving party. *MacKenzie v. City & County of Denver*, 414 F.3d 1266, 1273 (10th Cir. 2005).

Where, as here, the moving party asserts entitlement to judgment because a claim is preempted by federal law, the motion presents only a legal question for the court; if the court concludes that a state law claim is preempted, summary judgment is proper as to that claim. *Watters v. Wachovia Bank, N.A.*, 550 U.S.1, 20 (2007); *Dobbs v. Anthem Blue Cross & Blue Shield*, 475 F.3d 1176, 1177 (10th Cir. 2007).

Although the *Levine* did not review a summary judgment ruling, the court must apply the clear evidence standard to determine the propriety of granting summary judgment, as "'the inquiry involved in a ruling on a motion for summary judgment or

for a directed verdict necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits.'" *Gibson v. Weyerhaeuser Co.,* 35 F. App'x. 834, 836 (10th Cir. 2002) (unpublished opinion) (quoting *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252 (1986)).

As set forth in the court's summary judgment Order, the parties in this case do not dispute that Mr.Dobbs committed suicide in December 2002 after having taken Effexor for several days. At the time of his death, he was 53 years old. There is also no dispute regarding the facts underlying the medical diagnosis which led his physician to prescribe Effexor. Mr. Dobbs had seen a physician in December 2002 to inquire about medication for anxiety; he told his physician that he had encountered both health and financial problems, and was experiencing serious anxiety and depression. The physician described Mr. Dobbs as "fairly severely depressed," and he prescribed Lexapro, an antidepressant. Because Mr. Dobbs's condition did not improve, he again sought treatment; a different physician confirmed the diagnosis of severe depression. She instructed him to stop taking Lexapro, wait one day, and then begin taking Effexor. A few days later, Mr. Dobbs committed suicide. Plaintiff contends the Effexor label did not adequately warn of the suicide risk she contends was known to be associated with Effexor in 2002, thus rendering Wyeth liable under Oklahoma's common law failure-to-warn tort.

It is also not disputed that the FDA has the responsibility to regulate prescription drugs, including the authority to approve the content of labels and warnings accompanying such drugs. As more fully explained, *infra*, there is no dispute regarding the responsibility of the manufacturer to continually monitor the safety and efficacy of its prescription drugs, to study the effects of their use, and to regularly report findings to the FDA. Plaintiff does not dispute that Wyeth did so.

Plaintiff also does not dispute that the FDA has repeatedly conducted clinical studies and reviewed data regarding both the beneficial and potentially adverse effects of antidepressants, including Effexor, on patients in various age groups. Plaintiff concedes that the FDA has never approved an antidepressant suicidality warning for patients in Mr. Dobbs's age group; however, several years after his 2002 suicide, the FDA approved enhanced suicidality warnings for pediatric patients and, later, for adults under the age of 24.

The record in this case thus reflects that there is little dispute[2] regarding the factual record and the evidence. The question is whether the record contains clear evidence to warrant summary judgment based on preemption.

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[2] LCvR56.1 (c) states as follows:

> "The brief in opposition to a motion for summary judgment (or partial summary judgment) shall begin with a section which contains a concise statement of material facts to which the party asserts genuine issues of fact exist. Each fact in dispute shall be numbered, shall refer with particularity to those portions of the record upon which the opposing party relies and, if applicable, shall state the number of the movant's facts that is disputed. All material facts set forth in the statement of the material facts of the movant may be deemed admitted for the purpose of summary judgment unless specifically controverted by the statement of material facts of the opposing party."

Plaintiff's response to Wyeth's motion for summary judgment does not "begin with a section which contains a concise statement of material facts to which the party asserts genuine issues of fact exist." Instead, the factual portion of plaintiffs' response contains plaintiffs' exposition of "Facts Relevant to the 'Clear Evidence' Standard." Doc. no. 269, at 3. It does not appear that plaintiff takes issue with Wyeth's statement of undisputed facts. Wyeth's statement of undisputed facts is uncontroverted and is consequently taken as true. *See, e.g.* Bennett v. Fuller, 2008 WL 2987173, at *3 (N.D. Okla. 2008) (applying Northern District version of LCvR56.1). Although all of the facts in Wyeth's statement are taken as true, the facts which are dispositive are the facts set forth in this order.

Federal preemption and the impact of *Levine*:

Although there are three established types of federal preemption,[3] the parties agree that "conflict preemption" is the only potential basis for preemption in this case. Conflict preemption arises when "it is either impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution" of Congress's objective in enacting the subject federal law.[4] *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002).

Wyeth has consistently argued that it could not comply with both the duty to warn advanced by plaintiff and the FDA regulations without risking adverse action by the FDA because plaintiff contends that the state law duty to warn required Wyeth to include in the Effexor label a more extensive suicide warning than that which had been approved by the FDA. In fact, Wyeth contends the FDA in 2002 had rejected an enhanced suicidality warning for Effexor and similar antidepressants because it concluded scientific evidence did not support that warning.

Wyeth thus relies on what has been characterized as "impossibility preemption," a defense *Levine* described as "demanding." *Levine*, 129 S. Ct. at 1198. *Levine* did not, however, hold that impossibility preemption based on FDA labeling

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[3]The recognized categories are: 1) "express preemption," which exists when Congress has expressly stated that a federal law will preempt state law, *see English v. General Electric Co.*, 496 U.S. 72, 78-79 (1990); 2) "field preemption," which occurs when Congress has expressed its intent that federal law will exclusively occupy an entire field of regulation, *Id.*; and 3) "conflict preemption," which arises when "it is either impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002).

[4]Conflict preemption is not limited to federal statutes, but may be based on federal agency regulations. *Fidelity Federal Sav. And Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982). Furthermore, both state statutes and common law tort obligations may be preempted. *Geier v. American Honda Motor Co. Inc.*, 529 U.S. 861, 873 (2000); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521 (1992).

regulations is precluded in all cases. In fact, *Levine* recognized that, although FDA regulations authorize a manufacturer to expand label warnings without prior FDA approval under some circumstances, the "FDA retains authority to reject labeling changes made" under those circumstances. *Id.* Thus, the FDA labeling regulations do not preempt state law failure-to-warn claims unless the manufacturer presents "clear evidence that the FDA would not have approved a change" to the drug's label, thereby making it "impossible" for the manufacturer to comply with "both federal and state requirements." *Levine*, 129 S. Ct. at 1198.

A discussion of the facts of *Levine* is necessary to an understanding this court's ruling. *Levine* did not involve a failure-to-warn claim for Effexor or other antidepressants. At issue was the label warning and accompanying use instructions for Phenargen, an antihistamine approved by the FDA for the intravaneous treatment of nausea.[5] The plaintiff alleged that the manufacturer[6] violated its common law duty to warn of the risks associated with the injection of Phenargen, including the manner in which it is injected. The manufacturer argued that the claim was preempted because the FDA, exercising its regulatory authority to approve the content and use instructions for the drug's label, had previously approved the warning and use instructions on the Phenargen's label and had not dictated a change in those instructions. After the trial court rejected that argument, case proceeded to trial, and

[5] According to the facts discussed in *Levine*, the injectable form of Phenargen can be administered intravenously through an "IV-push" or "IV-drip" method. After receiving an IV-push injection of Phenargen, the plaintiff in *Levine* developed gangrene, resulting in the amputation of her arm. The drug had mistakenly been injected into her artery instead of her vein, resulting in severe infection. She sued Wyeth, the manufacturer, claiming in part that it failed to adequately warn clinicians of a known risk of accidental intra-arterial injection and failed to instruct them to use only the IV-drip method to avoid this risk. *Levine*, 129 S. Ct. at 1194.

[6] Wyeth was also the defendant manufacturer in *Levine.*

the jury returned a verdict for the plaintiff. The state appellate court affirmed, rejecting the manufacturer's preemption claim.

In affirming that decision, the Supreme Court held that the state failure-to-warn claim was not preempted by FDA regulations because the evidence did not support the conflicting obligations on which the manufacturer relied. The Court rejected the contention that, once a label is approved by the FDA, the manufacturer is not obligated to seek revision of its contents; it emphasized that FDA regulations permit a drug manufacturer, without first obtaining FDA approval, to strengthen a warning contained in a label previously approved by the FDA, if the manufacturer has evidence to support an enhanced or altered warning. *Levine*, 29 S.Ct. at 1196 (citing 21 C.F.R. §§ 314.70(c)(6)(iii)(A) and (C)). Although FDA approval must ultimately be obtained, the manufacturer can avoid still liability for improper labeling if it presents sufficient data to support the enhanced warning. *Id.* The Court further emphasized that, under the FDA regulatory scheme, "the manufacturer bears responsibility for the content of its label at all times," and is "required to revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.'" *Id.* at 1197-98 (quoting 21 C.F.R. § 201.80(e)).

In *Levine,* the Court found no evidence that the manufacturer had sought to enhance or alter the Phenargen label to include the warnings urged by the plaintiff, nor did the manufacturer argue "that it supplied the FDA with an evaluation or analysis concerning the specific dangers posed by" the Phenargen injection procedure at issue. *Levine*, 129 S. Ct. at 1199. Although it adopted a clear evidence standard, the Court found the manufacturer offered no evidence that the FDA had considered and rejected the warning at issue. Thus, it concluded the state law failure-to- warn claims were not preempted by the FDA regulations. *Id.*

As Wyeth suggests, this court's narrow basis for granting the original partial summary judgment motion is not impacted by *Levine* because it is essentially the same as that expressly recognized by *Levine* as warranting conflict preemption – the FDA would not have approved the label warnings urged by the plaintiff. Because *Levine* altered the standard of proof required to support that conclusion, however, the court must determine whether the Wyeth's evidence is satisfies the new standard.

Levine does not define "clear evidence," nor does it suggest the level of proof required to constitute such evidence. In fact, *Levine* found the manufacturer offered no evidence that the FDA would have rejected the proffered warning; thus, *Levine* "did not clarify what constitutes 'clear evidence.'" *Mason v.Smithkline Beecham Corp.*,596 F. 3d 387, 391 (7th Cir. 2010). As a result, "lower courts are left to determine what satisfies this 'clear evidence' standard in each case." *Schilf v. Eli Lilly and Company*, 2010 WL 3909909, at *4 (D. S.D. Sept. 30, 2010) (unpublished opinion).

Decisions addressing FDA conflict preemption after *Levine* do not contain precise definitions of clear evidence. Although those decisions have universally found the manufacturer's evidence inadequate to support conflict preemption, that result is not necessarily dictated here because application of the clear evidence standard is necessarily fact specific. Thus, the evidence in this case must be evaluated in the context of the FDA's regulation of the warnings accompanying antidepressants, including Effexor, as applied to the facts of this case.

FDA regulation of prescription drug labels:

Congress has authorized the FDA to regulate the prescription drug industry; that authority extends to, *inter alia*, pre-marketing approval of both a drug and the exact text of the proposed accompanying label, including any warnings, contraindications, or limitations on the drug's use. *See* 21 U. S. C. § 355; 21 C.F.R. § 314.105(b). FDA

regulations mandate the inclusion of a label warning section which "must describe clinically significant adverse reactions." 21 C.F.R. § 201.57(c)(6)(I). These include reactions that are potentially fatal, are serious even if infrequent, or those which can be prevented or mitigated through appropriate use of the drug in question. *Id.*

After a drug is approved by the FDA, manufacturers are required to maintain records, conduct additional testing as directed, and report to the FDA any significant adverse health consequences reported during the prescription drug's use. 21 U.S.C. §355(k)(1); 21 C.F.R. §§314.80 and 314.81. The FDA is statutorily responsible for continually monitoring the safety of approved drugs and is authorized to take actions including, *inter alia,* withdrawal of approval if scientific data indicates the drug is unsafe. 21 U. S. C. § 355(e). Approval must be withdrawn if the FDA finds that "clinical or other experience, tests or other scientific data show that such drug is unsafe for use;" approval must also be withdrawn where the FDA determines, "on the basis of new information," that the labeling for a drug "is false or misleading in any particular." *Id.*

As a general rule, once a label has been approved by the FDA, the manufacturer cannot change its content unless it submits a supplemental application to do so, and the FDA approves that supplemental application. 21 C.F.R. § 314.70(b). However, the FDA regulations contain an exception to the requirement of advance approval for label changes under certain circumstances; the provision is referred to as the "changes being effected" ("CBE") provision. *See* 21 C.F.R. § 314.70(c)(6)(iii). The CBE regulation allows a pre-approval label change by the manufacturer where the change is needed to add or strengthen a contraindication, warning, precaution or information about an adverse reaction. 21 C.F.R. § 314.70(c)(6)(iii)(A). The proposed change must be based on "reasonable evidence of" an association between

a hazard and the drug at issue; however, a causal relationship need not have been definitely established.. 21 C.F.R. § 201.57(c)(6)(I).

The CBE regulation was emphasized in *Levine* as an impediment to a manufacturer's preemption claim because it allows the manufacturer to alter its label to increase a warning without first obtaining FDA approval. As the Court explained:

> There is, however, an FDA regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" (CBE) regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

Levine, 129 S. Ct. at 1196 (citing 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C)). For this purpose, "'newly acquired information' is not limited to new data, but also encompasses 'new analyses of previously submitted data.'" *Levine*, 129 S. Ct. at 1197 (quoting FDA Notice of Final Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49604 (Aug. 22, 2008)). However, the FDA retains the authority to reject and require the manufacturer to remove such CBE label revisions where the risk, contraindication, or related alteration is not supported by "reasonable evidence of an association" with the prescription drug. 21 C.F.R. § 201.57(c)(6)(I).

FDA regulation of antidepressants, including Effexor:

The parties agree that Effexor is one of a class of drugs known as Selective Serotonin Reuptake Inhibitors ("SSRIs")[7], which are prescribed for the treatment of

[7]As Wyeth explains, Effexor is a serotonin and norepinephrine reuptake inhibitor, but for potential suicide-related risks, the FDA has treated SSRIs and Effexor as a class and required that they carry the same suicide labeling.

depression and similar conditions. Other drugs within the SSRI class include, *inter alia*, Paxil, Zoloft, and Prozac. The record also establishes that the FDA has consistently reviewed warning labels for SSRIs collectively, and its consideration of the proper content and scope of suicidality warnings has not been directed at specific brands of SSRIs, but at the entire classification.

As noted above, the FDA requires that a drug warning be based on "reasonable evidence of a causal association" between use of the drug and the hazard identified in the warning. 21 C.F.R. § 201.57(c)(6)(I). The FDA has consistently defined reasonable evidence of a causal association as "when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug." 44 Fed. Reg. 37434, 374634 (June 26, 1979).

The evidence before the court reflects the history of the FDA's position regarding the proper scope and content of suicidality warnings for SSRIs. The causal association required to support a hazard warning has repeatedly been considered by the FDA when assessing the propriety of including warnings in labels accompanying Effexor and other SSRIs. In particular, the FDA has repeatedly considered whether antidepressant labels should include statements mentioning the increased risk of suicide for patients taking antidepressants. In doing so, the FDA has consistently expressed concern that an enhanced suicidality warning not supported by scientific evidence creates a risk of "overall injury to the public health" resulting from the potential reduction in the use of antidepressants, thereby undermining the known benefit of such drugs in the treatment of depression. That concern was expressed in 1991, prior to the approval of Effexor. *See* Transcript of September 20, 1991 FDA

Wyeth Exs.1, 4, 5 and 6.

Psychopharmacologic Drugs Advisory Committee Meeting, Wyeth Ex. 1, pp. 124-33. Furthermore, the FDA continued to express the same concern in 2004, two years after Mr. Dobbs's suicide. January 5, 2004 FDA Memorandum, Wyeth Ex. 2, p. 3.

The FDA approved Effexor on December 28, 1993, after more than two years of analysis following Wyeth's submission of a New Drug Application ("NDA"). When approving Effexor, the FDA required Wyeth to include in the Effexor labeling and package insert a suicide precaution which the FDA required of all SSRI antidepressants at that time; that precaution stated in pertinent part:

> Suicide - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Effexor... should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Wyeth Ex. 20, December 28, 1993 FDA Approval Letter. The 2002 package insert for Effexor contained that same warning. *See* Wyeth Ex. 1 to original summary judgment motion. The package insert also reported that some patients in Effexor clinical trials experienced intentional self-injury, attempted suicide, and/or reported suicidal ideation. *Id.*

The FDA directed Wyeth to include in the "Adverse Reactions" section of the package insert the range of rates at which Effexor patients in clinical trials had experienced suicidal ideation and attempted suicide. Wyeth Ex. 20. The FDA also directed Wyeth to state in that section that "[i]t is important to emphasize that, although the events reported occurred during treatment with venlafaxine [the generic name for Effexor], there were not necessarily caused by it." *Id.*

The record reflects that, despite its continuing review of SSRI manufacturers' periodic reports of clinical trials and adverse events, the FDA continued to find no

scientific evidence of a causal connection between SSRIs and increased suicidality warranting an enhanced warning. It is undisputed that, in 1997, the FDA approved an NDA for an extended-release form of Effexor; it required the same warning language regarding suicide as that directed for the 1993 labeling insert. FDA approval letter of October 20, 1997, Wyeth Ex. 23. In 1999 and 2001, the FDA approved Wyeth's Supplemental New Drug Applications ("SDNAs") for Effexor. See Wyeth Exs. 24 and 25. Another SNDA for Effexor was approved in February of 2003, approximately two months after Mr. Dobbs' death. Wyeth Ex. 26. In the foregoing approvals of SNDAs, the FDA directed Wyeth to include the same language as appeared in the 1993 label warnings regarding suicide.

During this same time period, the FDA also approved more than a dozen NDAs and SNDAs for other SSRI prescription drugs, and each approval required the same language regarding suicide as was contained in the Effexor 1993package insert. *See* Wyeth Ex. 28. During the time period prior to and immediately following Mr. Dobbs's 2002 suicide, none of the FDA approvals required the addition of new or additional language regarding the risk of suicide resulting from taking SSRIs, including Effexor or its extended release version, Effexor-ER.

The record reflects that, following the approval of Effexor, Wyeth regularly submitted to the FDA the required reports reflecting suicide-related events; Wyeth submits as exhibits to its renewed brief copies of reports submitted during the time period of 1991 through 2003. Wyeth Exs. 12, 13, 14, 15, 16 , 17, 18, and 19. These reports were provided in accordance with the FDA's requirement that manufacturers regularly report such occurrences.

Although manufacturers are required to report such occurrences, the record reflects that the FDA has not considered individual manufacturers' reports of adverse events sufficiently persuasive to provide "reasonable evidence of an association"

between the drug and the reported adverse consequence. 21 C.F.R. § 201.57(e). With respect to SSRIs, the FDA has instead taken the position that the evidence required to support a label warning must be based on randomized, double-blind, controlled clinical trials. As early as 1991, the FDA Psychopharmacologic Drugs Advisory Committee ("PDAC") expressed the view that individualized data from manufacturers submitting reports of adverse effects is not sufficiently reliable to support the association required to warrant an enhanced label warning. The PDAC stated that "assessments of the potential of drugs to cause harm are ordinarily only deemed reliable in the scientific community if they are derived from clinical sources of evidence that allow a comparison, and it is a comparison of the incidence and intensity of events emerging in both the presence and the absence of drug treatment" that should be considered. Transcript of September 20, 1991 PDAC meeting, Wyeth Ex. 1, p. 125, lines 20-25; p. 126, line1. By 2004, that view had not changed, as Dr. Russell Katz, the Director of the FDA Division of Neuropharmacological Drug Products, testified before the PDAC that, with respect to data reflecting individual cases of suicidal behavior reported by companies marketing antidepressants, "we do not believe that this data can reasonably inform our judgment about any relationship between these drugs and suicidal behavior." Transcript of February 2, 2004 PDAC meeting, Wyeth Ex. 10, p. 23, line 25; p. 24, lines 1-6.

Wyeth's evidence also reflects the FDA's continued rejection of enhanced suicidality warnings for antidepressants during the time period following approval of Effexor. On three occasions prior to Mr. Dobbs's 2002 suicide, the FDA rejected citizen petitions asking it to strengthen the suicidality warnings for Prozac, an antidepressant regulated under the same SSRI classification as Effexor. On each occasion, the FDA rejected the requests, finding insufficient scientific evidence of an association between the SSRI and suicidality. See FDA Letter of July 26, 1991,

June 3, 1992 and June 25, 1997, submitted as Wyeth Exs. 27, 9, and 29, respectively. The 1997 citizen petition is the closest in time to Mr. Dobbs's suicide; that petition asked the FDA to require warnings indicating that patients who are considered at risk for suicide and who take Prozac should be carefully observed and should also consider taking a sedative. The FDA rejected that request, stating:

> The agency has continued to monitor carefully reports of a possible connection between Prozac and increased suicidality. However, no credible scientific evidence has caused the agency to depart from its conclusion that the current Prozac labeling appropriately reflects the level of concern about Prozac and suicidality.

Wyeth Ex. 29, p. 2. It is not disputed that the 1997 suicidality precaution in Prozac's label was the same as that approved for Effexor.

The FDA's view regarding suicidality and Effexor use did not change during the time period shortly before Mr. Dobbs's December 2002 suicide. The FDA's Acting Commissioner testified in a March 2004 Congressional hearing that, as of September 2002, the FDA had, on numerous occasions, "specifically considered and rejected such language as scientifically unsupportable and inconsistent with FDA determinations as to safety and effectiveness of the products." Wyeth Ex. 30, Hearings Before the U.S. House of Representatives Appropriates Committee, Subcommittee on Agriculture, Rural Development, FDA, and Related Matters, p. 85 (Mar. 11, 2004).

During 2002, the FDA completed additional reviews of data regarding SSRIs. In June, 2002, approximately six months prior to Mr. Dobbs's suicide, the FDA reported its conclusion that "[t]here were no significant differences in suicide rates between active treatments [on SSRIs] and placebo in any diagnostic category." Wyeth Ex. 37. In December 2002, at the request of the FDA, Wyeth submitted additional data from its clinical trials to be used in further FDA analyses. Wyeth Ex. 18.

However, when it reported the results of the analyses in 2003, the FDA stated that those results did not provide a scientific basis for a causal connection between SSRI use and suicidality. Wyeth Ex. 39.

In 2004, the FDA reported in a memorandum its conclusions based on analyses of studies involving "20 antidepressant drugs studied in 234 randomized controlled trials" of adults with major depressive disorder ("MDD"). Wyeth Ex. 2, January 5, 2004 FDA Memorandum, p. 4. The FDA reported its conclusion that "there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD." *Id.*

The reports preceding and immediately following Mr. Dobbs's 2002 suicide involve either conclusions for all age groups or, in the 2004 report, conclusions regarding adults. Mr. Dobbs was 53 years old in 2002, and no report during this time period found an increase risk of suicidality in his age group. Those conclusions are significant because, as a result of its subsequent ongoing analyses, the FDA concluded in 2004 there was sufficient scientific evidence to reflect an increased incidence of suicidal thinking or behavior in pediatric patients, classified as those under the age of 18, who had taken SSRIs. As a result of that determination, the FDA issued a May 5, 2005 Alert for Healthcare Professionals stating this conclusion. Wyeth Ex. 6. Thereafter, the FDA developed a revised label warning to reflect its determination regarding pediatric patients, and it directed SSRI manufacturers to include that warning in the label and package insert accompanying an SSRI.

After conducting further studies, the FDA's conclusion regarding pediatric patients was expanded to reflect a finding regarding adults age 24 and younger. That finding was based on a 2006 analysis in which the FDA, assisted by Columbia University researchers, analyzed 372 clinical trials involving nearly 100,000 patients. *See* Marc B. Stone & M. Lisa Jones, *Clinical Review: Relationship Between*

Antidepressant Drugs and Suicidality in Adults (Nov. 17, 2006), submitted as Wyeth Ex. 40. Based on that study, the FDA concluded that there was scientific evidence of an "increased risk of suicidality and suicidal behavior among adults younger than 25 years of age that approaches that seen in the pediatric population." *Id.*, p. 40. However, the FDA also concluded that the study reflected a "neutral" effect on suicidal behavior but a "possibly protective" effect for suicidality in "adults between the ages of 25 and 64," and a reduced risk of both suicidality and suicidal behavior in subjects aged 65 years and older. Wyeth Ex. 40, p. 44.

As a result of the 2006 studies and conclusions, the FDA directed manufacturers to modify the SSRI "black box"warnings previously approved for pediatric patients to report the foregoing conclusions regarding the incidence of suicidal thinking and behavior in young adults under age 25,[8] but to also state the studies "did not show an increase in the risk of suicidality with antidepresants..in adults beyond [age]24." May 2, 2007 FDA news release, Wyeth Ex. 8. In addition, the FDA required SSRI manufacturers to include in the warnings that the studies reflected a "reduction in risk with antidepressants...in adults aged 65 and older." Id. Thereafter, Wyeth incorporated these required "black box" warnings in its Effexor label. Wyeth Ex. 7. The evidence reflects that, since 2007, the FDA has not altered the text of the SSRI warning, and it remains in force.

The foregoing events are significant to the facts of this case for two reasons. First, the record reflects the FDA's ongoing study and analyses regarding the propriety of enhancing SSRI warnings to include the association between SSRIs and suicidality. That history is in contrast to the facts in *Levine*, in which the Court noted

[8]It had previously approved a "black box" warning for pediatric patients, and Wyeth incorporated that warning in its Effexor label. See Ex. 21 to Wyeth's original summary judgment motion.

that the trial court found the record reflected that, during the time period relevant to the claims asserted, neither the manufacturer or the FDA "gave more than passing attention" to the issue of the proper method for intravenous administration of Phenargen. *Levine*, 129 S. Ct. at 1199. Second, the record reflects that, despite the ongoing analyses from as early as 1993 through 2007, the FDA has yet to find scientific evidence to support the addition of a suicidality warning for patients in Mr. Dobbs's age group. After many years, the FDA concluded that scientific studies supported the issuance of a warning regarding pediatric patients; a few years later, it reach the same conclusion with respect to adults age 24 and younger. It did so only after numerous studies and, ultimately, an extensive analysis. Despite the scope of the 2006 analysis, however, it found no support for a suicidality warning applicable to the age group of which Mr. Dobbs was a member. To date, it has not done so. In fact, it has opined that the evidence suggests a neutral connection between SSRIs and suicidality in his age group.

The record also establishes that, during the time period preceding the FDA's decision to expand SSRI pediatric suicidality warnings, Wyeth had proposed an expanded warning based on its own internal studies. On September 25, 2002, Wyeth submitted the results of seven Effexor pediatric studies, accompanied by a proposed label alteration describing the rate of suicidality events and requesting an SNDA for pediatric use of Effexor. Wyeth Ex. 15. The FDA rejected that request and directed Wyeth not to add the proposed label change describing the negative pediatric studies; the FDA stated "we do not feel that it would be useful to describe these negative trials in labeling, since this may be misinterpreted as evidence that venlafaxine does not work in this population." Wyeth Ex. 44.

The record also shows that Wyeth subsequently utilized the CBE regulation to expand the suicidality warning for Effexor pediatric patients, based on its own

research. In August of 2003, Wyeth added to its label language reflecting a precaution based on increased reports of "suicide related adverse events such as suicidal ideation and self-harm" in pediatric patients. Wyeth Exs. 46 and 47. However, the FDA directed Wyeth to remove the language included in Wyeth's CBE enhanced label warning and to substitute FDA language applicable to all SSRIs at that time. Wyeth Ex. 48. According to the FDA, it did so because it did "not believe that a causal association between children taking [Effexor] and the emergence of suicidality has as yet been definitively established." *Id.*

Wyeth then proposed revised language, and asked the FDA to allow Effexor's label to continue to include a pediatric precaution; however, in a May 13, 2004 letter, the FDA again directed removal of Wyeth's language. Wyeth Ex. 49. At that time, the FDA had determined the requisite causal connection to support a pediatric precaution for SSRIs had been established; it required Wyeth and other SSRI manufacturers to utilize the label and warnings dictated by the FDA for all SSRIs, rather than those proposed by the manufacturers. *Id.* As discussed herein, that label included the FDA required statement that its studies did not show an increase in risk of suicidality in adults over the age of 24.

The record of the FDA's regulatory history with regard to SSRIs, including Effexor, establishes that the FDA continually reviewed individual manufacturers' reports of clinical trials and studies regarding suicidality; however, it relied on independent studies, rather than those of an individual manufacturer, to determine whether the required scientific basis existed to support an enhanced suicidality warning. Furthermore the lengthy regulatory history of SSRIs reflects the FDA's refusal to enhance such warnings without scientific evidence, as well as its reluctance to consider a warning which it believed might reduce the use of antidepressants and thereby undermine the benefits of their use in treating depression.

More important in the context of this case, however, is the FDA's repeated refusal to extend suicidality warnings to adult patients over the age of 25. In fact, the record reflects its repeated conclusions, during the time period preceding and following Mr. Dobbs's 2002 suicide, that there was no scientific evidence to support a causal connection between SSRI's and suicidality in adult patients.

The court finds the FDA's rejection of the pediatric warning added by Wyeth under the CBE regulations to be highly persuasive evidence. Despite Wyeth's efforts to expand the pediatric suicidality precaution, the FDA initially found insufficient scientific evidence to support that enhanced warning; even when it later determined that sufficient evidence existed to support the precaution, it did not approve Wyeth's Effexor-specific label alteration, but dictated a warning that was required of all SSRI manufacturers.

Given the evidence of record, the court finds there is clear evidence that the FDA would have rejected an expanded Effexor warning for patients in Mr. Dobbs's age group prior to his 2002 suicide. In fact, it continued to conclude that there was no evidence to support a warning for his age group as late as 2007, after additional studies were completed. The court finds that the record reflects clear evidence that the FDA would have rejected a 2002 warning of suicidality for 53-year-old Effexor patients.

In so finding, the court is aware that other courts applying the *Levine* clear evidence standard in the context of SSRI label warnings have universally rejected the manufacturers' evidence as insufficient.

The court has located five decisions in which a court applied the *Levine* evidentiary standard in a failure to warn case involving SSRIs. Two cases involve Effexor. Although other decisions apply the clear evidence standard to other

prescription drugs or other tort claims, the fact-specific nature of the evidentiary standard renders decisions other than SSRI labeling claims unpersuasive.

In *Mason v. Smithkline Beecham Corp.*, 596 F. 3d 387, 395 (7th Cir. 2010), the court found no preemption in a case involving a 23-year-old patient who committed suicide after taking Paxil. Although *Mason* acknowledged the FDA's repeated refusal to strengthen suicidal for SSRIs during the time period shortly before the 2003 suicide at issue, it also noted that, during the same time period, the FDA was considering scientific evidence that Paxil might increase suicidality in pediatric patients or young adults. In fact, it pointed to the evidence that such studies intensified shortly after the suicide, and led to enhanced warnings for pediatric patients and young adults within a relatively short time after Ms. Mason's suicide, concluding that these circumstances suggested the FDA would have approved a more extensive suicidality warning in 2003. *Id.*

The court, in *Mason*, also found unpersuasive some of the evidence submitted by Wyeth in this case. Specifically, it afforded little weight to the FDA's rejection of the three citizen petitions in the 1990's, finding the temporal gap between the last of the citizen petition rejections in 1997 and the 2003 suicide too great to suggest the FDA would have rejected a requested warning in 2003. *Id.* The court also gave "little weight" to the FDA regulatory history regarding Prozac, although it acknowledged the FDA treated all SSRIs as a class.

This court agrees with *Mason* that the FDA rejection of the citizen petitions is not, without more, sufficient because Mr. Dobbs's suicide, like that of Ms. Mason, occurred several years after 1997, and additional studies were conducted in the interim. However, the court does not agree with the Seventh Circuit's suggestion that the FDA would have treated individual SSRI manufacturers' label warnings differently, as the undisputed evidence in this case shows the FDA has consistently

treated all SSRIs the same and has, in fact, required the same suicidality labeling for all SSRIs. In fact, it rejected Wyeth's CBE label enhancement for pediatric patients and later required that all SSRIs labels include the same content for pediatric warnings.

Finally, this court finds it significant that the patient in *Mason* was 23 years old and, as the Seventh Circuit noted, the FDA's analysis of clinical studies during the time period near her suicide ultimately led to an enhanced warning for that age group. In contrast, none of its studies or analyses prior to, or after, Mr. Dobbs's suicide supported an enhanced suicidality warning for 53-year-old patients; in fact, the FDA expressly requires SSRI manufacturers to state in their product labels that studies reflect no evidence of a causal connection between antidepressants and suicidality in that age group.

In *Forst v. SmithKline Beecham Corp.*, 639 F. Supp.2d 948 (E.D. Wis. 2009), the court also rejected the manufacturer's evidence as insufficient to constitute clear evidence. Considering a claim based on the 2004 attempted suicide of a Paxil patient whose age is not disclosed, the court found it was not impossible for the manufacturer to seek FDA approval of an enhanced label warning. The manufacturer presented evidence that the FDA repeatedly concluded, between 1992 and 2004, that expanded suicidality warnings for SSRIs were "unwarranted and inappropriate." 639 F. Supp. 2d at 954. However, the court found such evidence insufficient to establish "impossibility preemption." According to *Forst*, "the fact that the agency considered the association between all SSRI's and suicidality on a number of occasions between 1992 and 2004...does not establish that the FDA would not have approved a proposed change in Paxil's labeling." *Id.* The court acknowledged "the FDA denied proposed label language in 2007, three years after Mr. Forst's attempted suicide." 639 F. Supp. 2d at 954. The court found that inadequate, however, because the FDA's rejection

"merely required removal of Paxil-specific language from a particular portion of Paxil's label in favor of uniform class-wide labeling for all SSRIs," and " did not preclude Paxil-specific language changes to other areas of the labeling or prevent [the manufacturer] from pursuing a label change through submission of a separate supplement." *Id.*

It is not clear whether the court in *Forst* was presented with the evidence, submitted in this case, that the FDA has consistently required uniform label warnings for all SSRIs. Thus, the evidence in this case supports the conclusion that the FDA would be highly unlikely to permit a brand-specific warning. In any event, the evidence in this case shows that Wyeth attempted on two occasions to utilize a label warning specific to Effexor, and those attempts were rejected by the FDA in favor of uniform language applicable to all SSRIs.

The claims in *Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142, 1159 (C. D. Cal. 2010), were based on the suicide of a 26-year-old man who had taken a generic form of Paxil.[9] Although the manufacturer submitted evidence that the FDA had refused enhanced Prozac suicide warnings during the relevant time period, the court described that evidence as showing only that there was a "mere possibility" the FDA "might not have allowed an enhanced suicidality warning" for Paxil. *Dorsett*, 699 F. Supp. 2d at 1159. Noting that there was no evidence the manufacturer had proposed an enhanced warning, the court found it offered only "theoretical assumptions of what the FDA would have done" if the manufacturer had proposed an enhanced warning; that was insufficient to satisfy the clear evidence standard required to support preemption. *Id.*

[9]Other courts have noted the distinction between FDA regulations governing brand-name prescription drugs and generic drugs. *Dorsett* did not discuss any differences in the regulations, and treated the claims as those a brand-name drug was at issue. Because generic drugs are not at issue in this case, the court need not discuss any possible differences in the FDA regulatory scheme.

This court finds *Dorsett* distinguishable because, unlike the manufacturer there, Wyeth does not rely in this case on a theoretical assumption of anticipated FDA action regarding an enhanced suicidality warning for older adults. Instead, it presents evidence that Wyeth proposed label alterations for pediatric patients which the FDA rejected and, when the FDA ultimately approved a warning for young adults, it required SSRI manufacturers to include a statement that studies did not support that warning for older patients.

In *Aaron v. Wyeth*, 2010 WL 653984, at * 6 (W. D. Pa. Feb. 19, 2010) (unpublished opinion), the court rejected Wyeth's preemption defense in a case involving the suicide of a 36-year-old man who had taken Effexor. In doing so, the court focused on *Levine's* characterization of "impossibility preemption" as a "demanding defense." 129 S.Ct. at 1199. The *Aaron* court examined the record to determine whether the manufacturer proved "it would have been impossible ...to place a warning on its Effexor other than the warnings in place at the time the antidepressant was prescribed." *Id.* at *6. According to *Aaron*, the manufacturer's evidence is insufficient to support preemption if it "does not definitively show that it was impossible for [the manufacturer] to enhance its safety warnings in place at the time." *Id.*

Although Wyeth presented evidence that it had proposed changes to the Effexor label warnings prior to 2005, and the FDA rejected those changes, the *Aaron* court found that evidence insufficient because Wyeth "did not press its position," but "acquiesced" to the FDA decision rejecting the enhanced warning. *Aaron,* 2010 WL 653984, at *6. The court did not discuss the FDA's regulatory history regarding SSRI suicidality warnings.

This court disagrees with *Aaron's* interpretation of the proof standard announced in *Levine.* Despite its reference to"impossibility preemption," *Levine* did

not characterize the proof standard as requiring a manufacturer in every case to prove that it would have been impossible to alter the drug's label. Instead, the standard announced is whether the manufacturer presents clear evidence that the FDA would have rejected the label alteration at issue. Furthermore, *Levine* expressly recognized that the FDA retains the authority to reject label changes made pursuant to the CBE regulation; this court does not interpret *Levine* as imposing upon the drug manufacturer a duty to continually "press" an enhanced warning which has been rejected by the FDA.

In *Baumgarner v. Wyeth Pharmaceuticals*, 2010 WL 3431671 (E. D. Pa. Aug. 31, 2010) (unpublished opinion), the court considered the claims of ten sets of plaintiffs who either took Effexor or were survivors of patients who committed suicide after taking Effexor in the time period from August 2000 to August 2003. The ages of the patients are not disclosed in the decision.

In rejecting preemption, the court examined only the evidence of the FDA's rejection of the three citizen petitions in the 1990's and Wyeth's proposed 2003 Effexor label change. The court adopted the plaintiffs' contention that the latter did not really show the FDA actually rejected the labeling change, but let it stand until the FDA adopted its own warning in 2004.[10] *Id.*, at *1.

Baumgarner did not discuss the FDA's conclusions regarding evidence of suicidality among different age groups or its requirement that manufacturers include,

[10]Plaintiff in this case also urges the court to reject Wyeth's contention that the FDA rejected its CBE proposal in 2003, noting that the altered label was in place for approximately seven months before the FDA directed Wyeth to remove it. However, as Wyeth points out, that warning was directed at pediatric patients, and occurred during the time period in which the FDA was re-evaluating its position regarding pediatric suicidality. Furthermore, as discussed, *supra*, even though that re-evaluation ultimately led to a pediatric and young adult suicidality warning, the FDA continued to require inclusion of a statement that there was no evidence of increased suicidality in adults between 25 and 64 years of age.

in pediatric and young adult suicidality warnings, a statement that there is no evidence of an association between Effexor and suicidality in patients over age 24. Instead, it cited *Mason*, *Forst*, and *Aaron*; without discussing the evidence presented in those decisions, the court concluded the "reasoning in those cases is persuasive," and held the claims were not preempted. *Id.*

For the foregoing reasons, this court finds these post-*Levine* decisions[11] to be distinguishable or unpersuasive (or both). The question in this case is whether Wyeth has presented clear evidence that, in 2002, the FDA would have rejected an enhanced suicidality warning for Mr. Dobbs, a 53-year-old patient taking Effexor. The court concludes that, given the specific circumstances presented in this action, Wyeth has satisfied the *Levine* evidentiary standard required to support preemption. Accordingly, plaintiff's claim that, in 2002, Wyeth had a duty to include on its Effexor label an enhanced suicidality warning for patients in Mr. Dobbs's age group is preempted.[12]

[11]Plaintiff argues that the Tenth Circuit and the Third Circuit have also rejected the evidence submitted by Wyeth as insufficient to satisfy *Levine*. The court disagrees. The Tenth Circuit's decision vacating and remanding this case did not analyze the evidence, but directed the court to do so in the context of the clear evidence standard. The Third Circuit decision in *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir. April 28, 2009)(slip opinion), also did not address the sufficiency of the manufacturer's evidence; instead, it vacated a prior judgment and remanded the consolidated cases to the courts to determine whether the *Levine* standard is satisfied. *See* Plaintiff's Ex. 15.

[12]As Wyeth points out in its reply, plaintiff's response brief suggests for the first time that the enhanced warning she seeks is one which would caution a "need for vigilance" upon initiation of Effexor treatment and state that patients should be closely observed for indications of violence or suicidality. The court agrees that plaintiff did not assert that claim, and has not previously characterized Mr. Dobbs's suicide as an episode of violence. As Wyeth suggests, even if plaintiff had done so, Effexor's label included a precautionary warning that "close supervision of high-risk patients should accompany initial drug therapy." Wyeth Ex. 20.

Conclusion:

For the foregoing reasons, Wyeth's motion for summary judgment is granted on plaintiff's failure-to-warn claim. This case will proceed on plaintiff's remaining claims.

IT IS SO ORDERED this 13th day of June, 2011.

STEPHEN P. FRIOT
UNITED STATES DISTRICT JUDGE

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